REMARKS

Amendments to the Claims

The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the instant application with the listing of claims currently provided. Claims 31, 32 and 34 were amended, Claims 35 and 36 were canceled and Claims 37-43 are new. Claims 1-30 and 33 were previously cancelled. The Applicants hereby state that all amendments do not add new subject matter to the specification.

Support for the compositions embraced by Claims 34 and 37 and the claims depending from these two independent claims can be found throughout the present specification, such as, *e.g.*, col 2, lines 14-16; col 8, lines 1-4; and Table 1.

Oath/Declaration

The Examiner objects to the submitted 37 C.F.R. §1.63 oath as allegedly being non-compliant pursuant to 37 C.F.R. §1.52(c) because non-initialed and/or non-dated alterations were made to the oath.

The Applicants acknowledge the Examiner's objection to the oath as being non-compliant pursuant to 37 C.F.R. §1.52(c) and are endeavoring to procure a new oath. However, more time is required as several of the inventors reside in England and Ireland. The Applicants wish to assure the Examiner that once received, the new oath will be promptly submitted.

Rejection Pursuant to 35 U.S.C. §112, ¶2 Indefiniteness

The Examiner has rejected Claim 32 as allegedly lacking definiteness under 35 U.S.C. §112, ¶2 stating that the term "active Clostridial neurotoxin" lacks antecedent basis. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The Applicants have amended Claim 32 and deleted the term "active". In addition, the Applicant's have added the phrase "a Clostridial neurotoxin light chain which has enzymatic activity for a target substrate selected from the group consisting of SNAP-25, VAMP and Cellubrevin." The Applicants respectfully submit that Claim 32 now has proper antecedent basis and request withdrawal of the 35 U.S.C. §112, ¶2 indefinite rejection.

Rejection Pursuant to 35 U.S.C. §101 Obviousness-type Double Patenting

The Examiner has provisionally rejected Claims 31 and 34-36 as allegedly being unpatentable over Claims 1-2, 6 and 8-9 of U.S. Patent 6,203,794, Dolly et al., *Modification of Clostridial Toxins for Use as Transport Proteins*, (Mar. 20, 2001), under the judicially created doctrine of obviousness-type double patenting under 35 U.S.C. §101. The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111.

The Applicants have amended Claims 31 and 34-36 to recite, in part, "a Clostridial neurotoxin light chain which has enzymatic activity for a target substrate." This limitation

distinguishes the invention of Claims 1-2, 6 and 8-9 from U.S. Patent 6203794, all of which are directed to "an inactive Clostridial toxin," wherein inactive means "a light chain containing one or more amino acid sequence mutations" that "inactivate its protease activity." (See independent Claim 1; col. 5, lines 3-6; Example 3; Example 4; Example 16; Example 17).

The Applicants respectfully submit that amended Claims 31 and 34-36 recite a patentablly distinct invention and request withdrawal of 35 U.S.C. §101 obviousness-type double patenting rejection.

Rejection Pursuant to 35 U.S.C. §102(e) Anticipation — Bizzini Patent

The Examiner has rejected Claims 31-32 and 34-36 as allegedly anticipated under 35 U.S.C. §102(e) by Bizzani et al., *Thiolated Polypeptide Compound Derived from a Tetanus Toxin Fragment, the Process for Obtaining and its Application*, U.S. Patent 4,594,336 (Jun. 10, 1986). Specifically, the Examiner contends that the Bizzani patent teaches "a composition comprising a tetanus toxin bound to a thiol group and that said composition could be used to transport agents (medicines) to the central nervous system." The Examiner further states that "since Bizzini et al., does not explicitly disclose the toxin used is "inactive", it is deemed, in absence of evidence to the contrary, to be active." (June 10, 2005 Office Action, page 6, bottom of second paragraph) The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111.

The Applicants respectfully submit that, contrary to the Examiner's assertion that the compositions disclosed in the Bizzini reference are active toxins, this patent clearly teaches that the disclosed toxins are indeed enzymatically inactive toxin fragments. Tetanus toxin is translated as a single chain polypeptide of approximately 150 kDa that is subsequently cleaved by proteolytic scission within a disulfide loop by a naturally-occurring protease. This posttranslational processing yields a di-chain molecule comprising an approximately 50 kDa light chain (LC) and an approximately 100 kDa heavy chain (HC) held together by a single disulfide bond and noncovalent interactions. Each mature di-chain molecule comprises three functionally distinct domains:

1) an enzymatic domain located in the LC (amino acids 1-457) that includes a metalloprotease region containing a zinc-dependent endopeptidase activity which specifically targets core components of the neurotransmitter release apparatus;

2) a translocation domain contained within the amino-terminal half of the HC (amino acids 458-879) that facilitates release of the LC from intracellular vesicles into the cytoplasm of the target cell; and

3) a binding domain found within the carboxyl-terminal half of the HC (amino acids 880-1315) that determines the binding activity and binding specificity of the toxin to the receptor complex located at the surface of the target cell.

The binding, translocation and enzymatic activity of these three functional domains are all necessary for toxicity. A toxin which lacks the activity of any one domain is inactive.

The tetanus toxin fragment disclosed in the Bizzini patent, designated B-II_b, is a 409 amino acid fragment of approximately 46 kDa (see, *e.g.*, Table I; col. 3, lines 52-55; col. 4, lines 3-10). This is in contrast to the full length Tetanus toxin which consists of 1315 amino acids and has a molecular weight of approximately 150 kDa (see, *e.g.*, the present application, page 1, lines 9-15). It is also made clear throughout the Bizzini patent that the B-II_b fragment retains the ability to specifically bind to the Tetanus receptors located on the surface of the neurons. For example on col. 9, lines 52-55, the Bizzini patent states, "This fragment, named B-II_b, ... is capable of binding to the gangliosides and to the synaptic membranes with an affinity which is even greater than that of tetanus toxin." Similar disclosure can be found at, *e.g.*, col. 6, lines 13-15; col. 11, lines 50-54; col. 11, lines 59-61; and col. 13, lines 19-21. Thus, the Bizinni disclosure indicates that the B-II_b fragment represents a fragment from amino acids 880-1315 comprising the binding domain of the full-length Tetanus toxin. Moreover, the Bizzini patent discloses that the B-II_b fragment lacks the proteolytic activity of full-length Tetanus toxin, a finding not surprising given that this fragments does not contain a light chain. For example in Table II, the enzymatic activity of the B-II_b fragment is reduced over a 1000-fold relative to the full-length toxin (compare the specific toxicity of the B-II_b fragment, which is 6.6×10^4 to that of the specific toxicity of the full-length Tetanus toxin, which is 7.8×10^7). Therefore, the B-II_b fragment disclosed in the Bizzini patent is a 409 amino acid fragment from the binding domain of tetanus toxin that retains the ability to bind to cell-surface receptors, but lacks the light chain and any enzymatic activity.

According to *MPEP* §2131, for a single prior art reference to anticipate a pending claim, that reference must teach each and every element of the pending claim in order to anticipate that claim. Claims 31-32 and 34-36 all recite a Clostridial toxin having, in part, a functional light chain, *i.e.* one having enzymatic activity for a target substrate. Since the toxin fragment compositions of the Bizinni patent lack a light chain, each and every element of the present claims are not anticipated. Therefore, the Applicants respectfully submit that the rejection is unsupported by the Bizzini reference and respectfully request withdrawal of the 35 U.S.C. §102(e) anticipation rejection against Claims 31-32 and 34-36.

Rejection Pursuant to 35 U.S.C. §102(e) Anticipation – Arnon Patent

The Examiner has rejected Claims 31-32 and 36 as allegedly anticipated under 35 U.S.C. §102(e) by Arnon, *Method to Prevent Side-Effects and Insensitivity to the Therapeutic Uses of Toxins*, U.S. Patent 5,562,907 (Oct. 8, 1996). Specifically, the Examiner contends that the Arnon patent discloses "recombinant toxins" comprising a botulinum neurotoxin and antibodies and optionally cation-channel blocking agents. The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111.

As stated above, for a single prior art reference to anticipate a pending claim, that reference must teach each and every element of the pending claim. The Arnon patent states that an immunotoxin is "a **targeting molecule** and a **toxin molecule** or moiety (including radioisotopes and pharmaceuticals)." (col. 13, lines 1-4), and:

> When immunotoxins are made by genetic engineering techniques that join the nucleic acid sequences of the **carrier molecule** and the **toxin molecule**, so that the

> **targeting protein** and **toxin** are covalently peptide-bonded together, the immunotoxin is sometimes referred to as a "recombinant toxin." (col. 13, lines 4-9)

Accordingly, the molecule disclosed in the Arnon patent contains a targeting molecule, a toxin molecule and a carrier molecule, where the targeting molecule is the antibody. However, the present claims recite, in part, "a Clostridial neurotoxin heavy chain which has binding specificity for a target nerve cell." Thus, the targeting function is an aspect of the toxin molecule and not the antibody molecule. In addition, the Clostridial toxins of the present claims do not recite a carrier molecule element. Thus, the Arnon reference does not anticipate the pending claims because this patent does not teach a Clostridial toxin targeting molecule and teaches additional elements not found in the present claims.

The Applicants respectfully submit that, contrary to the Examiner's assertion that the compositions containing cation-channel blocking agents disclosed in the Arnon reference are recombinant toxins, this patent teaches that the disclosed compositions are simply the admixture of a Botulinum toxin and a cation-channel blocking agent. For example, on col. 14, lines 57-60, the Arnon patent states, "combining Clostridium botulinum toxin(s) with a cation-channel blocking agents prolongs the duration of therapeutic muscle paralysis by blocking two or more separate steps in the nerve signalling pathway of muscle contraction." Nowhere does this patent disclose or teach a recombinant molecule comprising a botulinum toxin linked to a cation-channel blocking agent. Thus, the Arnon patent does not anticipate the pending claims because this reference does not teach a recombinant molecule comprising a Clostridial toxin and a cation-channel blocking agent.

Therefore, the Applicants respectfully submit that the rejection is unsupported by the Arnon reference and respectfully request withdrawal of the 35 U.S.C. §102(e) anticipation rejection against Claims 31-32 and 36.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Should the Examiner have any questions, he is invited to call the undersigned agent. Please use Deposit Account 01-0885 for the payment of the extension fees or any other fees due in connection with the current response.

Respectfully submitted,

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